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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/717,735	11/19/2003	Christopher R. Wagstrom	37210-8004.US00	8693

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EXAMINER	
STEELE, AMBER D	
ART UNIT	**PAPER NUMBER**
1639	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

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Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/717,735	**Applicant(s)** WAGSTROM ET AL.	
	Examiner Amber D. Steele	**Art Unit** 1639	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 01 December 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *4* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *01 December 2006*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☒ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-4,6,7,11,13,16-21,25,26,29-31 and 35*.
   Claim(s) withdrawn from consideration: *5, 8-10, 12, 14-15, 22-24, 27-2832-34, 36-38*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attached Advisory Action continuation.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

MARK L. SHIBUYA
PRIMARY EXAMINER

Advisory Action Continuation

1. The response to the final rejection received on December 1, 2006 has been considered but is not deemed to place the application in condition for allowance.

Status of the Claims

2. Claims 41-81 were canceled by Applicants in the preliminary amendment received on November 11, 2003.

Claims 39-40 were canceled by Applicants in the amendment received on August 29, 2005.

Claims 7 and 23 were amended in the amendment received on December 1, 2006. Claim 23 does not have the proper status identifier. The status identifier should be (currently amended, withdrawn) and not simply (withdrawn). The amendment to claim 7 has changed the scope of the claim so that the claim now reads on the elected species. Therefore, claim 7 is currently pending and under consideration. Thus the rejections have been reiterated below to include the limitations of claim 7.

Claims 1-38 are currently pending.

Claims 1-4, 6-7, 11, 13, 16-21, 25-26, 29-31, and 35 are currently under consideration.

Withdrawn Rejections

3. The rejection of claims 1-4, 6, 11, 13, 16-21, 25-26, 30, and 35 under 35 U.S.C. 102(b) as being anticipated by Griffiths *et al.* U.S. Patent No. 5,962,255 issued October 5, 1999 is withdrawn in view of the applicants' arguments.

4. The rejection of claims 1-4, 6, 11, 13, 16-21, 25-26, 30-31, and 35 under 35 U.S.C. 102(e) as being anticipated by Wang *et al.* U.S. Paten No. 6,833,441 B2 filed August 1, 2001 is withdrawn in view of applicants' arguments.

5. The rejection of claims 1-4, 6, 11, 13, 16-21, 25-26, 29-31, and 35 under 35 U.S.C. 103(a) as being unpatentable over Griffiths *et al.* U.S. Patent No. 5,962,255 issued October 5, 1999 and Goers *et al.* U.S. Patent No. 4,867,973 issued September 19, 1989 is withdrawn in view of applicants' arguments.

6. The rejection of claims 1-4, 6, 11, 13, 16-21, 25-26, 29-31, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang *et al.* U.S. Paten No. 6,833,441 B2 filed August 1, 2001 and Goers *et al.* U.S. Patent No. 4,867,973 issued September 19, 1989 is withdrawn in view of applicants' arguments.

Maintained Rejections

7. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejection - 35 USC § 102

8. Claims 1-4, 6-7, 11, 13, 16-21, 25-26, 30-31, and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by Ladner *et al.* U.S. Patent No. 5,223,409 issued June 29, 1993.

Ladner *et al.* teach binding proteins displayed on the outer surfaces of filamentous phage or cells (please refer to column 1, lines 40-52). Ladner *et al.* teach that the display system may be utilized to develop antibodies (please refer to column 15, lines 65-68) as further evidenced by

Ladner *et al.* (U.S. Patent No. 4,949,778 issued August 7, 1990; column 8, lines 62-67, column 15, lines 45-52, column 33, lines 56-68, and column 34, lines 1-57). In addition, Ladner *et al.* teach V_L-linker-V_H as single-chain antigen-binding fragment and V_L-C_L bound to V_H-C_{H1} as fragment antibodies (e.g. present claims 1-4 and 6-7; please refer to column 15, lines 34-64). Furthermore, Ladner *et al.* teach the display system as a binding domain operably linked to a signal sequence (e.g. OmpA and present claim 17; please refer to column 61, lines 39-53, column 62, lines 31-33, and column 63, lines 28-48) and a coat protein (e.g. M13 gene III and present claims 18 and 25; please refer to column 51, line 51 and column 54, lines 48-50) so that the expression product is transported to the inner membrane of the host cell (e.g. *E. coli* and present claims 25 and 35; please refer to column 56, lines 6-14 and column 61, lines 21-23) and trapped until the single-stranded DNA of the nascent phage particle collects both the wild type coat protein and the hybrid protein from the lipid bilayer and packages the hybrid protein into the surface sheath of the filamentous phage (e.g. M13 and present claims 19-21 and 25-26; please refer to column 54, lines 37-38 and column 55, lines 36-60) thereby exposing the hybrid protein on the replicable genetic package (please refer to column 51, lines 33-68 and column 52, lines 1-11). Lander *et al.* also teach the use of flexible linkers that encode a recognition site for a specific protease including Factor Xa (e.g. present claims 11, 13, 16 and 30-31, please refer to column 57, lines 39-59, column 58, lines 1-18, column 70, lines 64-68, column 71, lines 1-5, and column 73, lines 20-40). Therefore, one of ordinary skill in the art would have anticipated the present invention of claims 1-4, 6-7, 11, 13, 16-21, 25-26, 30-31, and 35 in view of the teachings of Ladner *et al.*

Arguments and Response

9. Applicants' argument directed to the rejection under 35 USC 102(b) as being anticipated by Ladner *et al.* U.S. Patent No. 5,223,409 issued June 29, 1993 for claims 1-4, 6-7, 11, 13, 16-21, 25-26, 30-31, and 35 was considered but are not persuasive for the following reasons.

Applicants allege that Ladner et al. does not teach a second polypeptide segment having therein a cleavable peptide sequence cleavable by a proteolytic agent. In addition, Applicants allege that Ladner et al. do not disclose subsequent association of the ipbd and the Pf3 coat protein upon protease cleavage.

Applicants' arguments are not convincing since the teachings of Ladner et al. anticipate the expression vector of the instant claims. It is the Examiner's position that Ladner et al. teach VL-linker-VH sequences with or without antibody conserved regions wherein VL is the first polypeptide segment, the linker is the second polypeptide segment, and VH is the third polypeptide segment (please refer to column 15). In addition, Ladner et al. teach that PBD/IPBD-linker-OSP wherein the PBD is the potential binding domain/first polypeptide, linker is the second polypeptide, and OSP is the outer surface protein/third polypeptide (please refer to columns 18, 55-58, 70-71). Additionally, Ladner et al. teach that the linkers can be cleavable via proteolytic agents (please refer to columns 57-58 and 70-71). Thus, in the case of VL-linker-VH (with or without additional constant regions) when the linker is cleaved the VL (first polypeptide) and VH (third polypeptide) can associate to form a multimeric polypeptide. Furthermore, the signal sequence is not relied upon as part of the evidence that the expression vector can be expressed on the surface of a genetically replicable package. Therefore, Ladner et al. teaches a second sequence that can be cleaved. Moreover, when the IPBD is VL-linker-VH

this structure can be combined with the outer surface protein (OSP) via an additional linker. Therefore, the VL is the first polypeptide, linker is the second polypeptide, VH is the third polypeptide, the second linker is the fourth polypeptide, and the OSP is the fifth polypeptide. Wherein the linker (second polypeptide) can be cleaved to allow for association of the VL and VH (particularly if a flexible linker is not utilized that would not permit the association of the VL and VH without cleavage) and the resulting multimeric polypeptide could still be linked to the OSP.

Claim Rejections - 35 USC § 103

10. Claims 1-4, 6-7, 11, 13, 16-21, 25-26, 29-31, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ladner *et al.* U.S. Patent No. 5,223,409 issued June 29, 1993 and Goers *et al.* U.S. Patent No. 4,867,973 issued September 19, 1989.

Ladner *et al.* teach binding proteins displayed on the outer surfaces of filamentous phage or cells (please refer to column 1, lines 40-52). Ladner *et al.* teach that the display system may be utilized to develop antibodies (please refer to column 15, lines 65-68) as further evidenced by Ladner *et al.* (U.S. Patent No. 4,949,778 issued August 7, 1990; column 8, lines 62-67, column 15, lines 45-52, column 33, lines 56-68, and column 34, lines 1-57). In addition, Ladner *et al.* teach V_L-linker-V_H as single-chain antigen-binding fragment and V_L-C_L bound to V_H-C_{H1} as fragment antibodies (e.g. present claims 1-4 and 6-7; please refer to column 15, lines 34-64). Furthermore, Ladner *et al.* teach the display system as a binding domain operably linked to a signal sequence (e.g. OmpA and present claim 17; please refer to column 61, lines 39-53, column 62, lines 31-33, and column 63, lines 28-48) and a coat protein (e.g. M13 gene III and present claims 18 and 25; please refer to column 51, line 51 and column 54, lines 48-50) so that

the expression product is transported to the inner membrane of the host cell (e.g. *E. coli* and present claims 25 and 35; please refer to column 56, lines 6-14 and column 61, lines 21-23) and trapped until the single-stranded DNA of the nascent phage particle collects both the wild type coat protein and the hybrid protein from the lipid bilayer and packages the hybrid protein into the surface sheath of the filamentous phage (e.g. M13 and present claims 19-21 and 25-26; please refer to column 54, lines 37-38 and column 55, lines 36-60) thereby exposing the hybrid protein on the replicable genetic package (please refer to column 51, lines 33-68 and column 52, lines 1-11). Lander *et al.* also teach the use of flexible linkers that encode a recognition site for a specific protease including Factor Xa (e.g. present claims 11, 13, 16 and 30-31, please refer to column 57, lines 39-59, column 58, lines 1-18, column 70, lines 64-68, column 71, lines 1-5, and column 73, lines 20-40).

However, Lander *et al.* do not teach a disordered region cleavable by urokinase.

Goers et al. *et al.* teach attachment of a therapeutic agent to antibodies via a linker which may be cleavable by urokinase (e.g. please refer to column 3, lines 14-31). Goers *et al.* further teach that the linker can be an amine, a branched linker, proteolytic peptide linkers cleavable by urokinase, or a linker may have a spacer and a cleavable portion of a random construction (e.g. present claim 11, 29-31; please refer to columns 21-22, Tables III-V and VII-VIII, Example: Series IV-V). Therefore, Goers *et al.* specifically teaches a urokinase cleavable linker.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the antigen-binding polypeptide display system of Ladner *et al.* and incorporate the urokinase peptide cleavage sequences of Goers *et al.*

One having ordinary skill in the art would have been motivated to do this because Goers *et al.* teaches that the linkage of the therapeutic agent to the antibody may interfere with antigen binding and potentially reduce the effectiveness of the therapeutic system, therefore, the use of a cleavage site to release the therapeutic agent from the antibody would be beneficial (please refer to column 4, lines 7-27 of Goers *et al.*). Furthermore, Lander *et al.* teach the use of flexible linkers that encode a recognition site for a specific protease including Factor Xa (e.g. present claims 16 and 30-31, please refer to column 57, lines 39-59, column 58, lines 1-18, column 70, lines 64-68, column 71, lines 1-5, and column 73, lines 20-40). Therefore, a urokinase cleavable peptide linker taught by Goers *et al.* could be utilized to increase antigen binding by the proteins displayed by genetically replicable packages taught by Ladner *et al.*

There is a reasonable expectation of success in the modification of the antibody display system taught by Ladner *et al.* with the urokinase cleavage sequence of Goers *et al.* because of the examples in Goers *et al.* showing the success of urokinase cleavable linkers joining antibodies to therapeutic agents or cells (please refer to sections 9.1-9.4 and 10.2-10.4 in Goers *et al.*).

Therefore, the modification of the antibody display system by Lander *et al.* with the urokinase cleavable sequence by Goers *et al.* would render the instant claims prima facie obvious.

Arguments and Response

11. Applicants' argument directed to the rejection under 35 USC 103(a) as being unpatentable over Ladner *et al.* U.S. Patent No. 5,223,409 issued June 29, 1993 and Goers *et al.*

U.S. Patent No. 4,867,973 issued September 19, 1989 for claims 1-4, 6, 11, 13, 16-21, 25-26, 30-31, and 35 was considered but was not found persuasive for the following reasons.

Applicants allege that one of skill in the art would not modify Ladner et al. to use a protease cleavage site between the protein of interest and a viral coat protein because Ladner et al. provides no teachings that upon protease cleavage, the gene of interest would assemble with the viral coat protein. In addition, applicants state that Ladner et al. is primarily interested in developing binding proteins which are not antibodies and thus Ladner et al. is not particularly concerned with the difficulties of developing anchored antibodies. Furthermore, applicants state that Goers is utilized to teach the urokinase peptide cleavage sequence only.

Applicants' arguments are not convincing since the combined teachings of Ladner et al. and Goers et al. render the expression vector of the instant claims *prima facie* obvious. It is the Examiner's position that Ladner et al. does state that the preferred embodiment for the binding domain is not antibody however Ladner et al. does teach phage display of antibodies as an embodiment. In addition, it is noted that the presently claimed invention is not limited to antibodies (e.g. a first polypeptide and a third polypeptide of the present claims do not implicitly suggest antibodies). Additionally, Ladner et al. still teaches that the expression vectors can be utilized for antibody expression (please refer to columns 15-16). Furthermore, Ladner et al. teach VL-linker-VH sequences with or without antibody conserved regions wherein VL is the first polypeptide segment, the linker is the second polypeptide segment, and VH is the third polypeptide segment (please refer to column 15). Furthermore, Ladner et al. teach that PBD/IPBD-linker-OSP wherein the PBD is the potential binding domain/first polypeptide, linker is the second polypeptide, and OSP is the outer surface protein/third polypeptide (please refer to

columns 18, 55-58, 70-71). Additionally, Ladner et al. teach that the linkers can be cleavable via proteolytic agents (please refer to columns 57-58 and 70-71). Thus, in the case of VL-linker-VH (with or without additional constant regions) when the linker is cleaved the VL (first polypeptide) and VH (third polypeptide) can associate to form a multimeric polypeptide. Furthermore, the signal sequence is not relied upon as part of the evidence that the expression vector can be expressed on the surface of a genetically replicable package. Therefore, Ladner et al. teaches a second sequence that can be cleaved. Moreover, when the IPBD is VL-linker-VH this structure can be combined with the outer surface protein (OSP) via an additional linker. Therefore, the VL is the first polypeptide, linker is the second polypeptide, VH is the third polypeptide, the second linker is the fourth polypeptide, and the OSP is the fifth polypeptide. Wherein the linker (second polypeptide) can be cleaved to allow for association of the VL and VH (particularly if a flexible linker is not utilized that would not permit the association of the VL and VH without cleavage) and the resulting multimeric polypeptide could still be linked to the OSP. Goers et al. is in fact utilized as evidence for a urokinase peptide cleavage sequence that can be attached to antibodies in order to ensure proper antigen binding (please refer to columns 3-4 and 21-22). Therefore, the teachings of Ladner et al. and Goers et al. render the instant claims *prima facie* obvious.

Future Communications

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amber D. Steele whose telephone number is 571-272-5538. The examiner can normally be reached on Monday through Friday 9:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ADS
December 15, 2006